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(AEPC). Eur Heart J 43:3997, 2022.

CHAPTER 264 Heart Failure: Pathophysiology and Diagnosis
Section 4 Disorders of the Heart,

Muscles, Valves, and Pericardium Michael M. Givertz, Mandeep R. Mehra

Heart Failure:

Pathophysiology and

Diagnosis CLINICAL DEFINITIONS, EPIDEMIOLOGY, AND PHENOTYPES ■ ■DEFINITIONS Heart failure (HF) is a common final pathway for most chronic car diovascular diseases including hypertension, coronary artery disease, and valvular heart disease. The American Heart Association/American College of Cardiology/Heart Failure Society (AHA/ACC/HFSA) guideline defines HF as a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood. The European Society of Cardiology's (ESC) definition emphasizes cardinal symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) due to a structural and/or functional abnormal ity of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise. An interna tional consensus conference proposed a universal definition of HF that is comprehensive and practical enough to encompass formal disease stages, with universal applicability, prognostic and therapeutic validity, and acceptable sensitivity and specificity (Fig. 264-1). Because some patients present without signs or symptoms of vol ume overload, the term heart failure is preferred over the older term

Symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality PART 6 Disorders of the Cardiovascular System and corroborated by at least one of the following Elevated natriuretic peptide levels or Objective evidence of cardiogenic pulmonary or systemic congestion FIGURE 264-1 Universal definition of heart failure (HF). This contemporary universal definition of HF is simple but conceptually comprehensive, with near universal applicability, prognostic and therapeutic validity, and acceptable sensitivity and specificity. (Reproduced with permission from B Bozkurt et al: Universal Definition and Classification of Heart Failure. J Card Fail 27:387, 2021.) congestive heart failure. Cardiomyopathy and left ventricular dysfunction are more general terms that describe disorders of myocardial structure and/or function, which may lead to HF. In pathophysiologic terms, HF has been defined as a syndrome characterized by elevated cardiac filling pressure and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction. Chronic heart failure describes patients with longstanding (e.g., months to years) symptoms and/or signs of HF typically treated with medical and device therapy as described in Chap. 265. Such patients are at risk of worsening heart failure, and when the episode resolves, the use of the term remission rather than stable HF is preferred, since these patients continue to retain the risk for further decompensation and sudden death. Acute heart failure, previously termed acute decom pensated HF, refers to the rapid onset or worsening of symptoms of HF. Most episodes of acute HF result from worsening of chronic HF, but ~20% are due to new-onset HF that can occur in the setting of acute coronary syndrome, acute valvular dysfunction, hypertensive

urgency, or postcardiotomy syndrome. Similarly, acute pulmonary edema in HF describes a clinical scenario in which a patient presents with rapidly worsening signs and symptoms of pulmonary congestion, typically due to severe elevation of left heart filling pressures. ■ ■EPIDEMIOLOGY Global Incidence and Prevalence HF is a major cause of mor bidity and mortality worldwide. An estimated 6.7 million American adults are being treated for HF, with >600,000 new cases diagnosed each year. Globally, it is estimated that 56.2 million people are living with HF with prevalence varying greatly by country. The prevalence of HF increases significantly with age, occurring in 1–2% of the population aged 40–49 years and 10% or more in adults >80 years old (Fig. 264-2). The lifetime risk of HF has increased to 24%; approxi mately one in four persons will develop HF in their lifetime. Projec tions based on National Health and Nutrition Examination Survey and U.S. Census Bureau data show that the prevalence of HF is expected to rise to 8.5 million Americans by 2030. According to the Nationwide Readmission Database, rates of HF hospitalizations in the United States declined from 2010 to 2014, followed by an increase from 2014 to 2017. HF readmissions after index hospitalization followed a similar trend. While prevalence of HF continues to rise, incidence may be decreasing due to improved recognition and treatment of cardiovascular disease

10.14%

6.96% Percent 4.93% 0.35% 1.73% 20–39 40–49 60–69 70–79 80+ FIGURE 264-2 Heart failure prevalence by age categories. Prevalence of heart failure among U.S. adults ≥20 years of age by age, from the National Health and Nutrition Examination Survey (NHANES), 2017–2020. (Reproduced with permission from B Bozkurt et al: J Card Fail 29:1412, 2023.) and its comorbidities as well as disease prevention. However, as rates of obesity rise globally, these favorable trends in HF incidence may reverse. There are distinct racial and ethnic differences in HF epidemiol ogy (Fig. 264-3). In community-based studies, black individuals have the highest risk of developing HF, followed by Hispanic, white, and Chinese Americans. These differences are attributed to disparities in cardiometabolic risk factors (e.g., obesity, hypertension, diabetes) as well as social determinants of health including socioeconomic status and access to health care. Similarly, studies have shown that age-adjusted rates of HF hospitalization are highest for black men, fol lowed by black women, white men, and white women. Accurate data on HF prevalence from emerging nations are lacking. As developing nations undergo socioeconomic development, the epidemiology of HF is becoming like that of Western Europe and North America, with coronary artery disease emerging as the most common cause of HF, although hypertension remains the highest population attributable risk for HF occurrence. Morbidity and Mortality In primary care, the overall 5-year sur vival following the diagnosis of HF is ~50%. For patients with severe HF, the 1-year mortality may be as high as 40%. In the United States, one in eight deaths list HF on the death certificate. The majority of these patients die of cardiovascular causes, most commonly progres sive HF or sudden cardiac death. A number of clinical and laboratory parameters are independent predictors of mortality (Table 264-1). In a population-based study, hospitalizations were common after an HF diagnosis, with 83% hospitalized at least once, and 67%, 54%, and 43% hospitalized at least two, three, and four times, respectively. Following an HF admission, mortality rates range from 8–14% at 30 days to 26–37% at 1 year to up to 75% at 5 years. Readmission with HF is also common, ranging from 20–25% at 60 days to nearly Incidence of HF in 1,000 Person (Years) 5.0 4.6 Median follow-up: 4.0 years (log-rank test: P=0.01) 4.5 4.0 3.5 3.5 3.0 2.4 2.5 2.0 1.5 1.0 1.0 0.5 Black 0.0 Hispanic White Race/Ethnicity Chinese FIGURE 264-3 Incidence of heart failure (HF). HF incidence rates by race/ethnicity in the

United States. (Reproduced with permission from IL Pina et al: J Am Coll Cardiol 78:2589, 2021.)

TABLE 264-1 Independent Predictors of Adverse Outcomes in Heart Failure Clinical Male sex Older age Diabetes mellitus Chronic kidney disease Coronary artery disease Advanced NYHA classa Presence of third heart sound or elevated JVP Decreased exercise capacity Cardiac cachexia Depression Structural Reduced left ventricular ejection fraction Reduced right ventricular ejection fraction Increased ventricular volumes and mass Secondary mitral or tricuspid regurgitation Hemodynamic Elevated pulmonary capillary wedge pressure Reduced cardiac index Reduced peak oxygen consumption Pulmonary hypertension Diastolic dysfunction Biochemical Worsening renal function Hyponatremia Hyperuricemia Elevated cardiac biomarkers (troponin and natriuretic peptides) Elevated plasma neurohormones (norepinephrine, renin, aldosterone, and endothelin-1) Electrophysiologic Tachycardia Widened QRS interval or LBBB Atrial fibrillation Ventricular ectopic activity Ventricular tachycardia and sudden death aSee Table 264-4. Abbreviations: JVP, jugular venous pressure; LBBB, left bundle branch block; NYHA, New York Heart Association. 50% at 6 months. With each subsequent admission, the risk of death rises. There are racial disparities in outcomes, with black patients having higher case–fatality rates compared to white patients. Men have higher age-adjusted mortality rates for death related to HF than women; and in the United States, mortality rate from HF varies by region (highest in Midwest) and population density (highest in rural areas). Despite these statistics, the overall prognosis for patients with HF is improving due to treatment of risk factors and increased use of guideline-directed therapies. Costs The overall cost of HF care is high (estimated $22.3 billion in the United States in 2018) and rising. Projections for 2030 are that hospitalization costs for HF in the United States will increase to $70 billion. Indirect costs due to lost work and productivity may equal or exceed this amount. The global economic burden of HF in 2012 was estimated at $108 billion, with direct costs accounting for 60%. For pediatric patients with acute HF, inpatient costs are estimated at $1 billion annually and rising. ■ ■PHENOTYPES AND CAUSES HF with Reduced Versus Preserved Ejection Fraction Epi demiologic studies have shown that approximately one-half of patients who develop HF have reduced left ventricular ejection fraction (EF; ≤40%), while the other half have near normal or preserved EF (≥50%) or are classified as having HF with mildly reduced EF (41–49%). Because most patients with HF (regardless of EF) have abnormalities in both systolic and diastolic function, the older terms of systolic heart

TABLE 264-2 Selected Causes of Heart Failure Heart Failure with Reduced Ejection Fraction Coronary artery disease Myocardial infarction Myocardial ischemia Nonischemic cardiomyopathy Infiltrative disorders Familial disorders Tachycardia induced CHAPTER 264 Valvular heart disease Aortic stenosis or regurgitation Mitral or tricuspid regurgitation Toxic cardiomyopathy Chemotherapy, immunotherapy Drugs such as hydroxychloroquine Alcohol, cocaine Heart Failure: Pathophysiology and Diagnosis
Congenital heart disease Intracardiac shunts Repaired defects Systemic right ventricular failure Chronic lung/pulmonary vascular disease Cor pulmonale Pulmonary arterial hypertension Infectious Chagas HIV Autoimmune disease Giant cell myocarditis Lupus myocarditis Heart Failure with Preserved Ejection Fraction Hypertension Coronary artery disease Valvular heart disease Aortic stenosis Mitral stenosis Restrictive cardiomyopathy Amyloidosis Sarcoidosis Hemochromatosis Glycogen storage disease Hypertrophic cardiomyopathy Radiation therapy Constrictive pericarditis Aging Myocarditis Endomyocardial fibroelastosis Obesity End-stage renal disease High-Output Heart Failure Thyrotoxicosis Arteriovenous shunt Obesity Cirrhosis Anemia Vitamin B deficiency

(beriberi) Chronic lung disease Myeloproliferative disorder Abbreviation: HIV, human immunodeficiency virus. failure and diastolic heart failure have been abandoned. Classifying patients based on their EF (HF with reduced EF [HFrEF], HF with mildly reduced EH [HFmrEF], or HF with preserved EF [HFpEF]) is important due to differences in demographics, comorbidities, and response to therapies (Chap. 265). Underlying causes of HF may be associated with reduced or preserved EF and include disorders of the coronary arteries, myocardium, pericardium, heart valves, and great vessels (Table 264-2). The diagnosis of HFpEF is often more challeng ing due to the need to rule out noncardiac causes of shortness of breath and/or fluid retention. HF with Recovered EF A subgroup of patients who are diag nosed with HFrEF and treated with guideline-directed therapy have rapid or gradual improvement in EF to the normal range and are referred to as having HF with recovered EF (HFrecEF). Predictors of HFrecEF include younger age, shorter duration of HF, nonischemic eti ology, smaller ventricular volumes, and absence of myocardial fibrosis. Specific clinical examples include fulminant myocarditis, stress car diomyopathy, peripartum cardiomyopathy, and tachycardia-induced cardiomyopathy, as well as reversible toxin exposures such as chemo therapy, immunotherapy, or alcohol. Despite recovery of EF, patients may remain symptomatic due to persistent abnormalities in dia stolic function, exercise-induced pulmonary hypertension, or related comorbidities (e.g., obesity). For patients who become asymptomatic, withdrawal of disease-modifying therapy can lead to recurrence of HF symptoms and decrease in EF in up to half of such patients within 6 months. In general, prognosis of patients with HFrecEF is superior to that of patients with either HFrEF or HFpEF.

Men Women Valvular disease Hypertension LVH 7% Diabetes 4% PART 6 Disorders of the Cardiovascular System 6% Angina pectoris 5% 39% 34% Myocardial infarction FIGURE 264-4 Population attributable risk of heart failure (HF) incidence. Based on longitudinal data from the Framingham Heart Study, the risk factors contributing most significantly to the population attributable risk (PAR) of HF in men were previous myocardial infarction and hypertension (in men, both represented equal contributions to HF PAR). In contrast, hypertension was the risk factor accounting for the majority of total PAR in women. In women, previous myocardial infarction accounted for only 13% of the PAR of HF compared with 34% in men. PAR values are developed based on individual calculations for each variable using hazard ratio and prevalence statistics. Thus, they may not, in aggregate, equal 100%. LVH, left ventricular hypertrophy. (Reproduced with permission from Givertz MM and Colucci WS. Heart failure. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. Philadelphia: Current Medicine; 2009.) HF with Mildly Reduced EF (HFmrEF) Patients with HF and an EF between 40 and 50% represent an intermediate group that are often treated for risk factors and comorbidities and with guidelinedirected medical therapy similar to patients with HFrEF. They are felt to have primarily mild systolic dysfunction, but with features of dia stolic dysfunction. They may also include either patients with reduced EF who experience partial improvement in their EF or those with ini tially preserved EF who suffer a decline in their systolic performance. The AHA/ACC/HFSA guideline requires evidence of spontaneous or provokable increased left ventricular filling pressures in their classifica tion of HFmrEF. Acquired Versus Familial, Congenital, and Other Disorders In developed countries, coronary artery disease is responsible for approximately two-thirds of the cases of HF, with hypertension as a principal contributor in up to 75% and diabetes mel litus in 10–40% (Fig. 264-4). Notably, population attributable risk for hypertension, obesity, diabetes mellitus, and coronary artery disease varies according to sex, race, and ethnicity (Fig. 264-5). While most cardiovascular disease underlying HF is acquired in mid and later life (Chaps. 272, 284, and 288), a wide range of congenital and

inherited disorders leading to HF may be diagnosed in children and younger adults. It is currently estimated that 13.3 million people globally and approximately 467,000 U.S. adults are living with congenital heart disease (CHD). In general, adults with CHD who develop HF can be divided into one of three pathophysiologic groups: uncorrected defects with late presentation due to missed diagnosis, nonintervention, or lack of access to care; repaired or palliated defects with late valvular and/or ventricular failure; or failing single-ventricle physiology. In addition, each adult with CHD often presents with unique anatomic and physiologic challenges that affect HF and its treatment. Inherited cardiomyopathies are also increasingly recognized in adults presenting with HF. These include more common disorders, such as hypertrophic and arrhythmogenic cardiomyopathies, and lesser known heart muscle disease related to pathogenic variants in genes encoding lamin and titin, muscular dystrophies, and mitochondrial disease. Most forms of familial cardiomyopathy are inherited in an autosomal domi nant fashion. Society guidelines have been published documenting the importance of taking a detailed three-generational family history and indications for (and limitations of) clinical genetic testing. A myriad of systemic diseases with cardiac and extracardiac manifestations (e.g., amyloidosis, sarcoidosis), autoimmune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis), infectious diseases (e.g., Chagas, HIV), and drug toxicities (chemotherapy, other prescribed or illicit agents) can result in HF with either reduced or preserved EF. In Africa and Asia, rheumatic heart disease remains a major cause of HF, especially in the young. Finally, disorders associated

Valvular disease Hypertension LVH 5% 8% Diabetes 12% 59% Angina pectoris 5% 13% Myocardial infarction with a high cardiac output state (e.g., anemia, thyrotoxicosis) are sel dom associated with HF in the absence of underlying structural heart disease. However, diagnosis and treatment of high-output HF will be missed if not considered in the differential diagnosis of patients with predisposing conditions (e.g., severe obesity, severe anemia, cirrhosis, end-stage renal disease with arteriovenous fistula, Paget’s disease, or nutritional deficiency such as beriberi). PATHOPHYSIOLOGY ■ ■PROGRESSIVE DISEASE HFrEF is a progressive disease that typically involves an index event followed by months to years of structural and functional cardiovas cular remodeling (Fig. 264-6). The primary event may be sudden in onset, such as an acute myocardial infarction; more gradual, as occurs in the setting of chronic pressure or volume overload (with valvular heart disease); inherited, as seen with genetic cardiomyopathies; or congenital disease in origin. Despite an initial reduction in cardiac performance, patients may be asymptomatic or mildly symptom atic for prolonged periods due to the activation of compensatory mechanisms (described below) that ultimately contribute to disease progression. Ventricular Remodeling As demonstrated in both animal and human studies, different patterns of ventricular remodeling occur in response to excess cardiac workload. Concentric hypertrophy, in which increased mass is out of proportion to chamber volume, effec tively reduces wall stress under conditions of pressure overload (e.g., hypertension, aortic stenosis). By contrast, an increase in cavity size or volume (eccentric hypertrophy) occurs in volume overload condi tions (e.g., aortic regurgitation, mitral regurgitation). In both forms of remodeling, an increase in ventricular mass is accompanied by changes at the cellular level with myocyte hypertrophy and interstitial fibrosis, at the protein level with alterations in calcium-handling and cytoskel etal protein abundance and/or function, and at the molecular level by reexpression of fetal genes (Table 264-3). In addition to cell loss from necrosis, myocytes that are unable to adapt to remodeling stimuli may be triggered to undergo apoptosis or programmed cell death. Further impairment in pump function and increased wall stress in the face of systemic vasoconstriction and loss of neurohormonal adaptation (discussed below) can lead to afterload

mismatch. These events feed back on remodeling stimuli, setting up a cycle of deleterious processes resulting in clinical HF. While our understanding of ventricular remodeling in HFrEF is well supported by animal and human studies, the mechanisms underlying HFpEF are less clear. The original descriptions of HFpEF focused on diastolic dysfunction as the primary mediator of HF

60.0 50.0 Population Attributable Risk (%) 40.9 39.0 40.0 30.0 25.8 22.3 20.0 14.8 9.6 12.1 10.1 10.1 10.0 0.0 Overall Caucasian African American Hispanic A

- ○ sum of PAR % within race/ethnicity may be greater than 100% as incidence rates are not adjusted for other risk factors 60.0 50.0 Population Attributable Risk (%) 42.7 40.7 40.0 30.0 20.0 12.0 13.6 7.1 10.8 9.2 10.0 0.0 Overall Caucasian African American Hispanic B
- ○ sum of PAR % within race/ethnicity may be greater than 100% as incidence rates are not adjusted for other risk factors FIGURE 264-5 Population attributable risk (PAR) for heart failure (HF) by race and ethnicity. PAR* by race and ethnicity for (A) HF with preserved ejection fraction (HFpEF) and (B) HF with reduced ejection fraction (HFrEF). *Sum of PAR% within race/ethnicity may be >100% as incidence rates are not adjusted for other risk factors. CHD, coronary heart disease. (Reproduced with permission from CB Eaton, M Pettinger, J Rossouw, LW Martin et al: Risk factors for incident hospitalized heart failure with preserved versus reduced ejection fraction in a multiracial cohort of postmenopausal women. Circ Heart Fail 9(10): e002883, 2016.) signs and symptoms as exemplified in older women with hyperten sion. At the myocyte level, impaired uptake of cytosolic calcium into the sarcoplasmic reticulum by reductions in adenosine triphosphate explained abnormalities in myocardial relaxation. As different phe notypes of HFpEF have emerged, many pathophysiologic processes that work in concert with each other, beyond diastolic dysfunction, have been implicated in disease progression, including vascular stiff ness, renal dysfunction, sodium avidity, and inflammation related to regional adiposity. Furthermore, biologic alterations including oxidative stress, impaired nitric oxide signaling leading to nitrosative stress, and insulin resistance may play a role in disease activity and inform future therapies. Autophagy is a natural process that removes unwanted cellular components by forming autophagosomes that fuse with lysosomes. While autophagy is deemed cytoprotective and adaptive, unchecked induction of autophagy may be maladaptive and a target by which disease-modifying therapy may exert beneficial effects.

53.6 CHAPTER 264 40.4 38.4 34.0 CHD Diabetes 25.0 Heart Failure: Pathophysiology and Diagnosis Hypertension Obesity 13.1 12.3 8.2 52.2 45.7 41.1 CHD 25.9 Diabetes Hypertension 19.0 16.5 Obesity 13.5 6.6 4.5 ■ ■MECHANISMS OF DISEASE PROGRESSION Several compensatory mechanisms become activated during the development of HF and contribute to disease progression. Our under standing of these mechanisms derives from preclinical studies, in vivo human studies, and randomized clinical trials demonstrating benefit of therapies targeted to attenuating or reversing these biologic processes. Neurohormonal Activation Activation of the sympathetic ner vous system (SNS) and renin-angiotensin-aldosterone system (RAAS) plays a critical role in the development and progression of HF. Initially, neurohormonal activation leads to increases in heart rate, blood pres sure, and cardiac contractility and retention of sodium and

water to augment preload and maintain cardiac output at rest and during exercise. Over time, these unchecked compensatory responses lead to excessive vasoconstriction and volume retention, electrolyte and renal abnormalities, baroreceptor dysfunction, direct myocardial toxicity, and cardiac arrhythmias. At the tissue level, neurohormonal activation

Remodeling stimuli Wall stress Cytokines Neurohormonal Oxidative stress Increased wall stress PART 6 Disorders of the Cardiovascular System Myocyte hypertrophy Ventricular enlargement Altered interstitial matrix Fetal gene expression Systolic or diastolic dysfunction Altered calcium-handling proteins Myocyte death FIGURE 264-6 Remodeling stimuli in heart failure. Chronic hemodynamic stimuli such as pressure and volume overload lead to ventricular remodeling through increases in myocardial wall stress, inflammatory cytokines, signaling peptides, neuroendocrine signals, and oxidative stress. The myocardium responds with adaptive as well as maladaptive changes. Reexpression of fetal contractile proteins and calcium handling proteins may contribute to impaired contraction and relaxation. Myocytes unable to adapt might be triggered to undergo programmed cell death (apoptosis). The net result of these changes is further impairment in pump function and increased wall stress, thus completing a vicious cycle that leads to further progression of myocardial dysfunction. (Reproduced with permission from Givertz MM and Colucci WS. Heart failure. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. Philadelphia: Current Medicine; 2009.) contributes to remodeling of the heart, blood vessels (atherosclero sis), kidneys, and other organs (Fig. 264-7) and the development of symptomatic HF. Landmark clinical trials in HF have demonstrated that antagonism of the RAAS and SNS with renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists, and beta blockers attenuates or reverses ventricular and vascular remodeling and reduces morbidity and mortality (Chap. 265). Vasodilatory Hormones While RAAS and SNS activation con tributes to disease progression in HF, a number of counterregulatory hormones are upregulated and exert beneficial effects on the heart, kidney, and vasculature. These include the natriuretic peptides (atrial TABLE 264-3 Mechanisms of Ventricular Remodeling Changes in Myocyte Biology Abnormal excitation-contraction coupling and crossbridge interaction Fetal gene expression (e.g., β-myosin heavy chain) β-Adrenergic receptor desensitization Myocyte hypertrophy Impaired cytoskeletal proteins Changes in Myocardial Composition Myocyte necrosis, apoptosis, and autophagy Interstitial and perivascular fibrosis Matrix degradation Changes in Ventricular Geometry Ventricular dilation and wall thinning Increased sphericity and displacement of papillary muscles Atrioventricular valve regurgitation

natriuretic peptide [ANP] and B-type natriuretic peptide [BNP]), prostaglandins (prostaglandin E1 [PGE1] and prostacyclin [PGI2]), bra dykinin, adrenomedullin, and nitric oxide. ANP and BNP are stored and released primarily from the atria and ventricles, respectively, in response to increased stretch or pressure. Beneficial actions are medi ated through stimulation of guanylate cyclase and include systemic and pulmonary vasodilation, increased sodium and water excretion, inhibition of renin and aldosterone, and baroreceptor modulation. Bradykinin and natriuretic peptides are inactivated by neprilysin, a membrane-bound peptidase, which explains in part the beneficial clinical impact of angiotensin receptor–neprilysin inhibition in HF (Chap. 265). As described below, natriuretic peptide levels can be used to assist in the diagnosis and risk stratification of patients with HF. Endothelin, Inflammatory Cytokines, and Oxidative Stress Endothelin is a potent vasoconstrictor peptide with growthpromoting effects that may play an important role in pulmonary hypertension and right ventricular failure. Endothelin is released from a variety of vascular and inflammatory cells within the pulmonary circulation and myocardium in response to

increased pressure and has direct deleterious effects on the heart, leading to myocyte hypertrophy and interstitial fibrosis. Unlike RAAS and SNS inhibition, however, endothelin blockade has not been shown to slow the progression of clinical HF due to left ventricular failure but is beneficial for treat ment of pulmonary arterial hypertension and consequent right HF (Chap. 294). Other factors that have the potential to cause or contrib ute to ventricular remodeling in HF include inflammatory cytokines such as tumor necrosis factor (TNF) α and interleukin (IL) 1β and reactive oxygen species such as superoxide and peroxynitrite. Potential sources of these biologically active substances are the liver and gastro intestinal tract, as described below. The role of anti-inflammatory and antioxidant therapies remains unproven. Novel Biologic Targets Sodium-glucose cotransporter 2 (SGLT-2) is a protein located on the proximal tubule of the kidney that is respon sible for reabsorption of up to 90% of filtered glucose. In patients with HF, activity of SGLT-2 contributes to sodium and water reten tion, endothelial dysfunction, abnormal myocardial metabolism, and impaired calcium handling. Inhibitors of SGLT-2 were developed for the treatment of type 2 diabetes mellitus to take advantage of their glycosuric and metabolic effects (Chap. 416). Subsequent large clini cal trials in cardiovascular disease including HF (with or without dia betes mellitus) have demonstrated not only safety of these agents (as required by the U.S. Food and Drug Administration) but also, more importantly, beneficial effects on morbidity and mortality. Whether benefits of SGLT-2 inhibitors in HF are due primarily to diuretic effects or to effects on cardiac and vascular remodeling, proarrhyth mia, renal function, and/or metabolic function, inflammation or dys regulated autophagy remains to be conclusively determined. Another pathway that is downregulated in HF and contributes to endothelial dysfunction involves cyclic guanosine monophosphate (cGMP). Oral soluble guanylate cyclase stimulators enhance the cGMP pathway and exert beneficial myocardial and vascular effects in experimental and clinical HF. Dyssynchrony and Electrical Instability In up to one-third of patients with HF, disease progression is associated with prolongation of the QRS interval. Electrical dyssynchrony in the form of left bundle branch block (LBBB) or intraventricular conduction delay results in abnormal ventricular contraction. As discussed in Chap. 265, cor rection of electrical dyssynchrony with left or biventricular pacing can improve contractile function, decrease mitral regurgitation, and reverse ventricular remodeling. In patients with symptomatic HFrEF and LBBB on guideline-directed medical therapy, cardiac resynchroni zation therapy or LBBB (or His bundle) pacing is suggested to reduce morbidity and mortality. Other forms of electrical instability, including atrial fibrillation with inadequate rate control and frequent prema ture ventricular complexes, can also contribute to worsening HF. In addition to the direct impact of tachycardia and irregular rhythm on disease progression, the link between these arrhythmias and cardiac

Baroreceptor dysfunction ↑ Sympathetic nervous system activity ↑ Vasopressin secretion ↓ Limb blood flow ↓ Renal blood flow ↑ Aldosterone secretion ↑ Sodium reabsorption ↑ Water reabsorption ↓ Limb blood flow FIGURE 264-7 Activation of neurohormonal systems in heart failure. Decreased cardiac output in heart failure (HF) results in an “unloading” of high-pressure baroreceptors (circles) in the left ventricle, carotid sinus, and aortic arch, which in turn causes reduced parasympathetic tone. This decrease in afferent inhibition results in a generalized increase in efferent sympathetic tone and nonosmotic release of arginine vasopressin from the pituitary. Vasopressin is a powerful vasoconstrictor that also leads to reabsorption of free water by the kidney. Afferent signals to the central nervous system also activate sympathetic innervation of the heart, kidney, peripheral vasculature, and skeletal muscles. Sympathetic stimulation of the kidney leads to the release of renin, with a resultant increase in circulating levels of angiotensin II and

aldosterone. The activation of the renin-angiotensin-aldosterone system promotes salt and water retention, peripheral vasoconstriction, myocyte hypertrophy, cell death, and myocardial fibrosis. Although these neurohormonal mechanisms facilitate short-term adaptation by maintaining blood pressure and organ perfusion, they also result in end-organ changes in the heart and circulation. (Modified from A Nohria et al: Atlas of Heart Failure: Cardiac Function and Dysfunction, 4th ed, WS Colucci [ed]. Philadelphia, Current Medicine Group, 2002, p. 104, and J Hartupee, DL Mann: Nat Rev Cardiol 14:30, 2017.) remodeling (atrial and ventricular) involves increased wall stress, neu rohormonal activation, and inflammation. Secondary Mitral Regurgitation A large number of patients with HFrEF demonstrate evidence of mitral regurgitation. This occurs due to a distortion in the mitral valve apparatus and includes the effects of various pathophysiologic mechanisms including reduced contractile force, which leads to decreased coaptation of the leaflets, a spheri cal shape of the ventricle that influences length and function of the chordal-papillary muscle structure, increased dimension of the mitral annulus (and inability of the annulus to contract during systole) with reduced leaflet alignment, and dilation of the posterior wall of the left atrium, which distorts the posterior leaflet of the valve. This worsening in regurgitant volume contributes to progression in HF and adversely influences prognosis. Ensuring that this vicious cycle is interrupted is now a therapeutic target in HF. Some success has been noted by treating the mitral valve using transcatheter techniques when patients are carefully selected after exposure to optimal medical therapy when residual and significant secondary mitral regurgitation persists. Simi larly, progressive tricuspid regurgitation can result from and promote adverse right ventricular remodeling. Current interventional studies are underway to assess the impact of transcatheter tricuspid valve repair or replacement in patients with advanced HF. ■ ■CARDIORENAL AND ABDOMINAL INTERACTIONS An important concept underlying the pathophysiology of HF recog nizes the systemic nature of disease. Thus, while the primary hemo dynamic problem in HF is related to abnormalities in myocardial function (preload, afterload, and contractility), many of the present ing signs and symptoms are related to end-organ failure, including dysfunction of the kidneys, liver, and lungs. The heart and kidney interaction increases circulating volume, worsens symptoms of HF, and results in disease progression, referred to as the cardiorenal syndrome. Traditionally, this relationship was deemed to be a consequence of an

↓ Afferent inhibitory signals CHAPTER 264 Vasomotor center Heart Failure: Pathophysiology and Diagnosis
↑ Angiotensin II ↑ Renin secretion impairment in forward flow (cardiac output) leading to a decrease in renal arterial perfusion, worsening renal function, and neurohormonal activation with release of arginine vasopressin, resulting in water and sodium retention. However, evidence has emerged that renal dysfunc tion may not be adequately explained simply by arterial underfilling and a decline in cardiac output. Systemic venous congestion in HF with increased backward pressure may be operative in determining the development of the cardiorenal syndrome, and relief of venous conges tion is associated with significant improvement in renal function in HF. Increased intraabdominal pressure, as noted in right-sided HF, and a rise in abdominal congestion are correlated with renal dysfunc tion in worsening HF. The interaction is not only confined to the renal component of the abdominal compartment but also involves the liver and spleen. The splanchnic veins serve as a blood reservoir and actively function in regulation of cardiac preload during changes in volume status, regulated by transmural pressure changes or mechanisms of systemic sympathetic activation. The liver and spleen participate in determining volume regulation in HF in addition to several additional interactive pathways. Splanchnic congestion results in portal vein dis

tension and activation of the hepatorenal reflex as well as the spleno renal reflex, which induces renal vasoconstriction. Thus, decongestion in HF by diuretic therapy or mechanical means such as ultrafiltration reduces volume, but also facilitates a decrease in pressure within the abdominal compartment, and this combination of therapeutic effect may serve to improve or stabilize renal function in HF. ■ ■GUT CONGESTION, THE MICROBIOME, AND INFLAMMATION As noted above, circulating levels of proinflammatory cytokines are elevated in a number of cardiovascular disease states, including HF, and have been associated with disease progression. While the primary source of inflammation is unknown, emerging evidence suggests that an alteration in gut microbial composition and loss of microbial diver sity may play an important role. The potential role of gut congestion

and also altered gut microbial composition may propagate the chronic state of inflammation and immune system dysregulation, eventu ally leading to progression of HFrEF. Lipopolysaccharide (LPS) is a gram-negative bacterial cell wall product whose levels are increased in patients with HF in the setting of increased intestinal permeability during periods of congestion, which is reduced with diuretic treatment. LPS is a strong stimulator of the immune system and can lead to dys regulated systemic inflammation via macrophage activation. Resulting increases in cytokines such as TNF-α, IL-1, and IL-6 in these pathways can cause progressive loss of cardiac function and also contribute to cardiac cachexia. A mechanistic link has been shown between gut microbe–dependent generation of trimethylamine N-oxide derived from specific dietary nutrients such as choline and carnitine and poor outcomes in patients with both acute and chronic HF. Microbegenerated uremic toxins, such as indoxyl sulfate, may play an impor tant role in the development of HF, particularly in interaction with renal insufficiency. Thus, bowel ischemia and/or congestion depending on HF severity may be associated with morphologic and functional alterations in the intestines and result in bacterial endotoxemia and a proinflammatory state.

PART 6 Disorders of the Cardiovascular System ■ ■HIGH-OUTPUT STATES Although most patients with HF, with either reduced or preserved EF, have low or normal cardiac output (CO) accompanied by elevated sys temic vascular resistance (SVR), a minority of patients with HF pres ent with a high-output state with low SVR (Table 264-2). High-output states by themselves are seldom responsible for HF, but their develop ment in the presence of underlying cardiovascular disease can precipi tate HF. For example, chronic anemia is associated with high CO when hemoglobin reduces significantly, for example, to a level that is ≤8 g/dL. An increase in vasodilatory metabolites and arteriolar vasodilation in response to decreased oxygen-carrying capacity of the blood in addi tion to a decrease in blood viscosity contributes to low SVR. Even when severe, anemia rarely causes high-output HF in the absence of a specific cardiac abnormality such as ischemic or valvular heart disease. Patients with end-stage renal disease (Chap. 323) are at particular risk of developing high-output HF when chronic anemia is exacerbated by increased flow through an arteriovenous fistula. In a recent analysis of the National Readmission Database, the most common causes of highoutput HF included pulmonary disease (19.8%), severe obesity (9.9%), sepsis (9.6%), cirrhosis (8.9%), myelodysplastic syndrome (7.9%), hyperthyroidism (5.5%), and sickle cell disease (3.3%). EVALUATION ■ ■HISTORY Symptoms of Congestion: Pulmonary Versus Systemic The most common symptoms of HF are related to volume overload with elevation in pulmonary and/or systemic venous pressures. Shortness of breath is a cardinal manifestation of left HF and may arise with increas ing severity as exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and dyspnea at rest. Mechanisms of dyspnea include pulmo nary venous congestion and transudation

of fluid into the interstitium and/or alveoli, leading to decreased lung compliance, increased airway resistance, hypoxemia, and ventilation/perfusion mismatch. Stimula tion of juxtacapillary J receptors leading to an increased ventilatory drive and reduced blood flow to respiratory muscles may cause lactic acidosis and a sensation of dyspnea. The New York Heart Associa tion (NYHA) functional classification (Table 264-4) may be used to categorize patients based on the amount of effort required to provoke breathlessness. Notably, however, NYHA class does not correlate well with other objective measures of cardiac structure (e.g., left ventricular size, EF) or function (e.g., peak oxygen consumption). Shortness of breath when bending forward (e.g., to put on socks or tie a shoe) has been associated with an increase in cardiac filling pressure, especially in the presence of a low CO, a symptom referred to as “bendopnea.” Orthopnea refers to dyspnea that occurs in the recumbent position and is due to redistribution of fluid from the abdo men and lower body into the chest, increased work of breathing due

TABLE 264-4 New York Heart Association Functional Classification FUNCTIONAL CLASS LIMITATION CLINICAL ASSESSMENT Class 1 None Ordinary physical activity does not cause undue fatigue, dyspnea, palpitations, or angina. Class II Mild Comfortable at rest. Ordinary physical activity (e.g., carrying heavy packages) may result in fatigue, dyspnea, palpitations, or angina. Class III Moderate Comfortable at rest. Less than ordinary physical activity (e.g., getting dressed) leads to symptoms. Class IV Severe Symptoms of heart failure or angina are present at rest and worsen with any activity. to decreased lung compliance, and, in patients with ascites or hepato megaly, an elevation of the diaphragm. Orthopnea typically occurs in the awake patient within 1–2 min of lying down and may be relieved by raising the head and chest with pillows or an adjustable bed. With more severe HF, patients may end up sleeping in a recliner chair or sitting up, although for some, orthopnea may diminish as symptoms of right HF appear. Orthopnea may be accompanied by nocturnal cough related to pulmonary congestion. Paroxysmal nocturnal dyspnea (PND) refers to episodes of short ness of breath that awaken a patient suddenly from sleep with feelings of anxiety and suffocation and require sitting upright for relief. In con trast to orthopnea, PND usually occurs after prolonged recumbency, is less predictable in occurrence, and may require 30 min or longer in the upright position for relief. Episodes are often accompanied by coughing and wheezing (so-called cardiac asthma) thought to be due to increased bronchial arterial pressure leading to airway compression and interstitial pulmonary edema causing increased airway resistance. Acute pulmonary edema, due to marked elevation of the pulmonary capillary wedge pressure, is manifested by severe shortness of breath and pink, frothy sputum (Chap. 316). Cheyne-Stokes respiration and central sleep apnea may precipitate episodes of PND in HF and are related to increased sensitivity of the respiratory center to arterial PCO_2 and a prolonged circulatory time. Unlike obstructive sleep apnea, which can be treated with positive airway pressure, oral appliance, or surgical therapy, central sleep apnea has no proven therapy beyond the directed treatment of HF (Chap. 308). In contrast to symptoms of left HF due to pulmonary venous con gestion, symptoms of right HF are typically related to systemic venous congestion. Weight gain and lower extremity edema may be the initial manifestations followed by a range of gastrointestinal symptoms due to edema of the bowel wall and hepatic congestion. Abdominal bloating, anorexia, and early satiety are common. Some patients develop right upper quadrant pain related to stretching of the hepatic capsule with consequent nausea and vomiting. When these symptoms are associated with abnormal liver function tests (see below), misdiagnosis of bili ary tract disease may occur. For patients with refractory right HF, the development of massive edema involving the entire body with recur rent pleural effusions and/or ascites is termed anasarca. Symptoms of Reduced

Perfusion Some patients with advanced HF present with symptoms related to decreased CO, sometimes referred to as low-output syndrome. Fatigue and weakness, particularly of the lower extremities, are nonspecific symptoms that can occur with exertion or at rest. Pathophysiology includes reduced blood flow to exercising muscles with endothelial dysfunction and increased SVR from neurohormonal activation. Chronic alterations in skeletal muscle structure and metabolism have also been demonstrated. In older patients with HF and cerebrovascular disease, reduced systemic perfu sion may result in mental dullness, depressed affect, and confusion. In addition to low CO, fatigue may be caused by volume depletion, hypo natremia, iron deficiency, and medication effect (e.g., beta blockers). Other Symptoms Patients with HF may present with mood distur bances and poor sleep, both of which may be exacerbated by nocturnal

TABLE 264-5 Precipitating Factors in Heart Failure Patient-Related Excess exertion or emotional stress Excess fluid and/or sodium intake Nonadherence with medications Heavy alcohol use Provider-Related Use of medications that cause salt and water retention (e.g., NSAIDs) Prescribed use of medications with negative inotropic properties (e.g., CCBs) Unrecognized congestion and inadequate use of diuretics Heart Failure–Related Uncontrolled hypertension Myocardial ischemia or infarction Atrial or ventricular arrhythmias Pulmonary embolism Other Disease States Systemic infection Worsening renal or hepatic failure Hyperthyroidism Untreated sleep apnea Anemia or iron deficiency syndrome Abbreviations: CCB, calcium channel blocker; NSAID, nonsteroidal antiinflammatory drug. dyspnea and obstructive and/or central sleep apnea. Nocturia due to improved CO and renal perfusion in the supine position, in addition to delayed diuretic effects, can also contribute to sleep disturbances. Oliguria due to severe reductions in renal blood flow may be a sign of advanced-stage HF. Precipitating Factors Patients with HF may be asymptomatic or mildly symptomatic either because the cardiac impairment is mild or because compensatory mechanisms help to balance or normalize cardiac function. Symptoms of HF may develop when one or more precipitating factors increase cardiac workload and disrupt the bal ance in favor of decompensation. Specific factors may be identified in 50–90% of admissions and can be divided into patient-related factors, provider-related factors, HF-related disease states, and other causes (Table 264-5). Inability to recognize and correct these factors promptly may lead to persistent HF despite adequate treatment. ■ ■PHYSICAL EXAMINATION General Appearance Most patients with mild-moderate HF will appear well nourished and comfortable at rest. Even patients with more advanced disease may be in no distress after resting for a few minutes but may demonstrate immediate dyspnea with limited exertion such as walking across the room. In contrast, patients with severe HF may need to sit upright and appear anxious, diaphoretic, and dyspneic at rest with pallor due to anemia or duskiness due to low output. Other signs of severe HF include cool extremities and peripheral cyanosis. Cardiac cachexia (Table 264-6), defined partially as unintentional edema-free weight loss of >5% over 12 months, may be observed in patients with longstanding, severe HF as bitemporal or upper body muscle wast ing. Contributing factors include poor oral intake due to anorexia, decreased fat absorption due to bowel wall edema, and catabolic/meta bolic imbalance from activation of inflammatory cytokines (see above) and dysregulation of the growth hormone–insulin-like growth factor 1 pathway. Rarely, scleral icterus and jaundice may result from severe right HF. Others may demonstrate frailty, which can be diagnosed in the presence of sarcopenia and is exemplified by poor hand-grip strength or severely reduced gait speed. Vital Signs With new-onset HF, heart rate rises and blood pressure may initially be increased due to sympathetic activation. In patients

TABLE 264-6 Diagnostic Criteria for Cachexia in Adults • Underlying disease and body weight loss ≥5% in ≤12 months (or BMI <20 kg/m2) • Plus at least three of the following five criteria • Decrease in muscle strength • Fatigue • Anorexia • Low fat-free mass index • Abnormal biochemistry: inflammation, anemia, low serum albumin levels CHAPTER 264 Abbreviations: BMI, body mass index. Source: Reproduced with permission from S von Haehling et al: Nat Rev Cardiol 14:323, 2017. Heart Failure: Pathophysiology and Diagnosis

with chronic HF on guideline-directed medical therapy, resting heart rate ideally should be <70–75 beats/min, and blood pressure should be in the normal to low-normal range. An irregular rhythm may be due to atrial fibrillation or flutter or frequent premature atrial or ventricular complexes. Severe HF may be associated with hypotension and narrow pulse pressure along with a rapid, thready pulse. An alternating strong and weak pulse, known as pulsus alternans, is attributed to reduced left ventricular contraction in every other cardiac cycle due to incomplete recovery causing reduction in the left ventricular stroke volume with each alternate beat. Respiratory rate may be normal at rest but may increase on lying down or on minimal exertion. Advanced HF may be associated with periodic breathing or Cheyne-Stokes respirations. The patient is usually unaware of the altered breathing pattern, but family members or friends may become alarmed or attribute this incor rectly to anxiety. Oxygen saturation is typically normal on room air unless there is acute pulmonary edema, underlying CHD with shunt ing, severe pulmonary arterial hypertension, or concomitant acute or chronic lung disease. A low-grade fever resulting from cytokine activation may occur in severe HF and subside when compensation is restored. Jugular Venous Pulse Examination of the jugular veins provides an estimate of the right atrial pressure. Typically, the patient is exam ined at a 45° angle, and jugular venous pressure (JVP) is quantified in centimeters of water by estimating the height of the venous column of blood above the sternal angle in centimeters and then adding 5. In patients with mild right HF, JVP may be normal at rest (≤8 cm H_2O) but increase with compression of the right upper quadrant. Hepato jugular reflux is elicited by applying firm continuous pressure over the liver for 15–30 s while observing the neck veins. The patient must breathe normally and not strain during the maneuver. Higher levels of venous pressure approaching the angle of the jaw are common in chronic right HF. If significant tricuspid regurgitation is present, prom inent V waves and Y descents may be noted. The abdominojugular test, defined as an increase in right atrial pressure during 10 s of firm mida bdominal compression followed by an abrupt drop on pressure release, suggests elevated left-sided filling pressure. Elevation in JVP during inspiration or Kussmaul’s sign may be due to severe biventricular HF and is a marker of poor outcome; it can also be seen with constrictive pericarditis or restrictive cardiomyopathy. Lung Examination Pulmonary rales result from transudation of fluid from the intravascular space into the alveoli and airways. In gen eral, rales are heard at the lung bases, but in severe HF or acute pulmo nary edema, they may be heard throughout the lung fields. Wheezing and rhonchi can occur with congestion of the bronchial mucosa and sometimes lead to a misdiagnosis (and inappropriate treatment) of asthma or chronic obstructive pulmonary disease (COPD). Rales may be absent in patients with longstanding HF and chronically elevated pulmonary capillary wedge pressures due to increased lymphatic drainage, which prevents spillage from the interstitium into the alveoli. In biventricular or predominant right HF, bilateral pleural effusions are recognized as dullness to percussion and decreased breath sounds at the bases. When pleural effusions are unilateral, they typically involve the right side.

Cardiac Examination As discussed above, chronic HF with ven tricular remodeling is typically accompanied by cardiac enlargement. The apical impulse is displaced downward and to the left

and may be diffuse in dilated cardiomyopathy or sustained in pressure overloaded states such as aortic stenosis. In biventricular or severe right HF, a right ventricular heave or parasternal lift may be palpated along the left sternal border. Uncommonly, a palpable third heart sound may be present. In patients with HFpEF, precordial palpation is often normal. On auscultation, an S3 gallop is most commonly present in patients with volume overload and tachycardia, suggests severe hemodynamic compromise, and carries negative prognostic significance. An S4 gallop is not specific to HF but may be present in patients with HFpEF due to hypertension. Holosystolic murmurs of mitral and tricuspid regurgita tion are present in the setting of advanced HF, often in the absence of structural valvular abnormalities. In patients with secondary pulmo nary hypertension, a loud pulmonary component of the second heart sound may be heard. Abdomen and Extremities Hepatomegaly is an early sign of systemic venous congestion. The liver edge may be tender due to stretching of the capsule, but with progression of right HF, tender ness may disappear. The liver edge may be pulsatile in patients with tricuspid regurgitation. Longstanding hepatic congestion may result in cardiac cirrhosis with congestive splenomegaly and mild-moderate ascites. The presence of massive ascites should lead to a search for other causes such as constrictive pericarditis or primary liver failure. Dependent lower extremity edema is common in chronic HF and is typically symmetric and pitting. Over time, chronic edema may cause reddening and induration of the skin, become weeping, or lead to cellulitis. Anasarca is used to describe massive, generalized edema involving the legs, sacrum, and abdominal wall. In patients with acute HF or younger adults with chronic HF, lower extremity edema may be absent despite marked systemic venous hypertension. Unilateral lower extremity edema may be due to deep venous thrombosis, prior trauma, or history of vein harvest for bypass surgery. Nonpitting edema that does not respond to increasing doses of diuretics may represent lymphedema that requires alternative diagnostic workup and treatment.

PART 6 Disorders of the Cardiovascular System ■ ■DIAGNOSIS The diagnosis of HF is relatively straightforward when the patient presents with typical signs and symptoms; however, the signs and symptoms of HF are neither specific nor sensitive. It is therefore important for clinicians to have a high index of suspicion for HF, par ticularly in patients who are at increased risk, including older patients with underlying cardiovascular disease and those with comorbidities such hypertension, diabetes, and chronic kidney disease. In this set ting, additional laboratory testing and imaging should be performed (Fig. 264-8). Routine Laboratories Standard laboratory testing in patients with HF includes a comprehensive metabolic panel, complete blood count, coagulation studies, and urinalysis. Selected patients should have assessment for diabetes, hyperlipidemia, and thyroid function. Blood urea nitrogen and creatinine levels are often elevated in mod erate-severe HF due to reduced renal blood flow and/or increased renal venous pressure. Worsening renal function (Chaps. 321 and 322) due to diuretics, RAAS inhibitors, and noncardiac medications (e.g., nonsteroidal anti-inflammatory drugs) is also common. Pro teinuria may be present in the setting of longstanding hypertension or diabetes or suggest an underlying systemic disease. Chronic right HF with congestive hepatomegaly can lead to modest elevations in transaminases, alkaline phosphatase, and bilirubin that should not be confused with biliary tract disease. Marked elevation in transaminases and lactic acid suggests cardiogenic shock with severe low output. In patients with cardiac cirrhosis, hypoalbuminemia may exacerbate fluid accumulation, whereas hyperammonemia contributes to altered mental status. In general, inflammatory markers such as erythrocyte sedimentation rate, C-reactive protein, and uric acid are nonspecific and do not aid in the diagnosis of HF. Other laboratories, including

History and physical examination Laboratories Chest x-ray Electrocardiogram Echocardiogram Determine cause Risk stratification CMR/CT/PET Ischemia/viability imaging Tissue characterization Coronary angiography Angina or ischemia Chest pain or risk factors Screening for: Hemochromatosis Amyloidosis Sarcoidosis Endomyocardial biopsy NYHA functional class Cardiopulmonary exercise test Natriuretic peptide level Ambulatory rhythm monitor Hemodynamics Family history FIGURE 264-8 Initial assessment of patients presenting with heart failure. The initial evaluation starts with a thorough history and physical examination, focusing on detection of comorbidities including hypertension, diabetes, and hyperlipidemia. In addition, identification of valvular heart disease, vascular disease, history of mediastinal radiation, or exposure to cardiotoxins (e.g., chemotherapy, alcohol, or illicit drugs) may help determine underlying cause. A family history of sudden death, heart failure, arrhythmias, or cardiomyopathy is also useful. Routine laboratory evaluation (see text) should also be performed. Chest x-ray is useful to detect cardiomegaly and fluid overload and to rule out pulmonary disease. A 12-lead electrocardiogram should be performed to detect abnormalities of cardiac rhythm and conduction, left ventricular hypertrophy, and evidence of myocardial ischemia or infarction. Two-dimensional echocardiography with Doppler imaging is indicated to assess cardiovascular structure and function and detect abnormalities of the myocardium, heart valves, or pericardium. Further imaging and laboratory studies aimed at identifying a specific cause of cardiomyopathy depend on information obtained from the history and physical examination. In all patients, risk stratification should be performed to assess severity of illness, guide therapy, and provide prognosis to patient and family. CMR, cardiac magnetic resonance imaging; CT, computed tomography; NYHA, New York Heart Association; PET, positron emission tomography. antinuclear antibodies, rheumatoid factor, serum free light chains, serum protein electrophoresis, ferritin, ceruloplasmin, hepatitis C, and HIV, are reserved for targeted testing. Electrolyte abnormalities seen in HF include hyponatremia due to sodium restriction, diuretic therapy, and vasopressin-mediated free water retention. Hyponatremia is a negative prognostic indicator at the time of HF hospitalization and predicts decreased long-term sur vival (Table 264-1). Hypokalemia is most often due to thiazide or loop diuretics given without oral potassium supplementation but may also result from increased aldosterone levels. Hyperkalemia may result from marked reductions in glomerular filtration rate and is exacerbated by use of RAAS inhibitors, potassium-sparing diuretics, and potassium supplements (Chap. 265). Hypo- or hyperkalemia may lead to atrial or ventricular arrhythmias. Hypophosphatemia and hypomagnesemia are commonly associated with chronic alcohol use. Anemia is not diagnostic of HF, but when present, it may exacerbate underlying ischemic heart disease or decrease quality of life in patients with HF due to any cause and should be corrected. Rarely, severe

anemia may cause high-output HF typically in the presence of under lying cardiovascular disease. The presence of iron deficiency (with or without anemia) is increasingly recognized in patients with chronic HF and has been attributed to decreased gut absorption, impaired hepatic storage, and chronic blood loss. Repletion with IV iron (but not oral iron) results in improved symptoms and exercise capacity and reduced HF hospitalizations, but its effect on survival remains uncertain. Chest X-Ray Major abnormalities on chest imaging associated with left HF include enlarged cardiac silhouette (cardiothoracic ratio >0.5) and pulmonary venous congestion. Early radiologic signs of acute HF include upper zone venous redistribution and thickening of interlobu lar septa. When the pulmonary capillary wedge pressure is moderate to severely elevated, alveolar edema can present as diffuse haziness extending downward toward the lower lung fields. The absence of these

findings in patients with chronic HF reflects the increased capacity of the lymphatics to remove interstitial and/or pulmonary fluid. Pleural effusions of varying size and distribution are common in biventricular HF. Chest x-ray can also be used to identify noncardiac causes of dys pnea (e.g., pneumonia, COPD). Electrocardiogram No specific electrocardiographic (ECG) pat tern is diagnostic of HF. Rather, the ECG may provide important information regarding presence of underlying cardiac disease. For example, left ventricular hypertrophy and left atrial enlargement suggest HFpEF due to hypertension, aortic stenosis, or hypertrophic cardiomyopathy. The presence of Q waves or infarction is suggestive of ischemic heart disease, whereas Q waves with reduced QRS voltage (pseudo-infarct pattern) may be seen with restrictive or infiltrative cardiomyopathies (e.g., amyloid). Conduction system disease should raise concern for cardiac sarcoid or Chagas cardiomyopathy in the right clinical setting. Paroxysmal or persistent atrial fibrillation is present in up to 40% of patients with chronic HF and is an indication for anticoagulation. Premature ventricular complexes (PVCs) and nonsustained ventricular tachycardia can reflect worsening HF and are markers of increased risk. Conversely, frequent PVCs can cause cardiomyopathy that may be treated successfully with ablation (Chap. 260). Finally, determination of the QRS width and presence of LBBB is used to ascertain whether the patient may benefit from cardiac resynchronization or left bundle branch (or His bundle) pacing therapy. Noninvasive Imaging Noninvasive cardiac imaging (Chap. 248) is essential for the diagnosis, evaluation, and management of HF. Two-dimensional echocardiography provides an accurate and rapid determination of ventricular size and function and valvular mor phology and function and can detect intracavitary thrombi and pericardial effusions. When left ventricular ejection fraction (LVEF) is ≥50%, systolic function is deemed to be normal. Myocardial strain rate imaging using speckle tracking can add incremental value to LVEF and carries prognostic value. Doppler techniques can be used to estimate CO, pulmonary artery pressures, and valve areas, and may detect abnormalities in left ventricular diastolic filling in patients with HFpEF. For patients with end-stage HF, echocardiography is critical for assessment of right ventricular function before and after mechanical circulatory support and heart transplant. Transesopha geal echocardiogram (TEE) or cardiac computed tomography (CT) with contrast is indicated to rule out left atrial appendage thrombus prior to cardioversion and can assess aortic or mitral valve pathology in planning for transcatheter valvular replacement or repair. TEE can also be used to assess for endocarditis in patients with bacteremia or acute valvular regurgitation. Cardiac magnetic resonance imaging (CMR) has emerged as a highly accurate and quantitative tool for evaluation of left ventricular mass, volumes, and function and for determining specific causes of HF (e.g., ischemic cardiomyopathy, myocarditis, amyloidosis, hemochro matosis). CMR is particularly helpful in defining multiple anatomic and functional abnormalities in adults with CHD. Serial CMR studies can assess ventricular remodeling in response to therapy and are useful in clinical research. For patients who cannot undergo CMR (e.g., due

to implantable devices), cardiac CT is particularly helpful to rule out pericardial disease or left ventricular apical thrombus. Coronary CT angiography has also emerged as a useful noninvasive test to rule out obstructive coronary artery disease as a cause of HF. While limited by availability and cost, cardiac positron emission tomography (PET) plays a role in evaluating the extent of ischemia, infarction, or hibernat ing myocardium in patients with coronary artery disease and, in the case of sarcoidosis, can reliably determine the severity and distribution of cardiac inflammation.

CHAPTER 264 Cardiopulmonary Exercise Testing While not routinely per formed in HF, cardiopulmonary exercise testing using a symptomlimited, ramp protocol can provide an objective assessment of peak functional capacity in patients being evaluated for mechanical circu latory support or heart transplant (Chap. 271). Several parameters including absolute and percent-predicted peak oxygen consumption (VO2) and ventilatory efficiency (VE; assessed by the VE/VCO2 slope) are independent predictors of survival. Additional data including heart rate and blood pressure response to exercise and exercise-induced arrhythmias can also be assessed. This test may also be useful in defin ing the cause of dyspnea when the diagnosis is uncertain. Heart Failure: Pathophysiology and Diagnosis

Biomarkers Circulating levels of natriuretic peptides are useful, adjunctive tools in the diagnosis of HF. BNP and N-terminal pro-BNP (NT-proBNP) are released from the atria and ventricles in response to increased wall stress. Patients with HFrEF tend to have higher levels than patients with HFpEF, whereas levels may be falsely low in obesity. In ambulatory patients with dyspnea, the measurement of BNP or NTproBNP is useful to support clinical decision-making regarding the diagnosis of HF, especially in the setting of clinical uncertainty or with concomitant lung disease. Moreover, natriuretic peptide levels can be used to establish disease severity and prognosis in chronic HF and may help to guide optimal dosing of medical therapy in stable outpatients. Importantly, many noncardiac factors, including age, female sex, and chronic kidney disease, increase natriuretic peptide levels. Other car diovascular diseases including atrial fibrillation, pulmonary embolism, and pulmonary arterial hypertension can also increase BNP levels. Galectin-3 and soluble ST2 (suppression of tumorigenicity 2 protein) are newer biomarkers that have been approved for assessment of prog nosis in HF but are not widely used. Biomarkers of renal injury require further study in HF, although use of cystatin C to measure renal func tion may be more accurate than a creatinine, which can be influenced by muscle mass. Invasive Studies In the intensive care setting, assessment of cardiac filling pressures and CO may be necessary to differentiate cardiogenic from noncardiogenic pulmonary edema and manage hemodynamic instability. Placement of a pulmonary artery catheter can be performed safely at the bedside and used to determine response to intravenous vasoactive and diuretic therapy in severe HF. Simultaneous measure ment of right and left heart filling pressures in the cardiac catheterization laboratory can be used to distinguish restrictive cardiomyopathy from constrictive pericarditis. Coronary angiography is indicated to exclude ischemic heart disease as an underlying, potentially reversible cause of left ventricular dysfunction. The management of coronary artery disease in the setting of chronic HF is discussed in Chaps. 285–287. If echocardiographic windows are suboptimal, left ventriculography can provide an assessment of left ventricular size and function and severity of mitral regurgitation. The role of right ventricular endomyocardial biopsy in the management of HF and cardiomyopathy remains con troversial. Indications include detection of myocarditis (lymphocytic, eosinophilic, sarcoid, or giant cell), diagnosis of cardiac amyloidosis and chemotherapy- or immunotherapy-related left ventricular failure, and screening for cardiac allograft rejection following heart transplant. COMORBIDITIES ■ ■DIABETES Type 2 diabetes mellitus is a risk factor for the development of HF (Table 264-7) and increases the risk of morbidity and mortality in

TABLE 264-7 Mechanisms That Contribute to Development of Heart Failure in Patients with Type 2 Diabetes Mellitus Altered myocardial substrate Abnormal mitochondrial bioenergetics Oxidative stress and inflammation PART 6 Disorders of the Cardiovascular System Lipotoxicity Endoplasmic reticulum stress Impaired insulin signaling β2-Adrenergic receptor signaling G protein–coupled

receptor kinase 2 signaling RAAS activation Advanced glycation end products Autophagy Abbreviation: RAAS, renin-angiotensin-aldosterone system. Source: Modified with permission from TA Zelniker: Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. J Am Coll Cardiol 75:422, 2020. patients with established disease. In ambulatory HF cohorts, the preva lence of diabetes ranges from 10 to 40%, with prevalence even higher in patients hospitalized with HF. When the two diseases coexist, patients are at increased risk for adverse outcomes, worse quality of life, and higher costs of care. Recent data from cardiovascular outcomes trials demonstrate that HF is a critical outcome in patients with diabetes and that glucose-lowering therapies can impact morbidity and mortal ity. As discussed above, SGLT-2 inhibitors in particular have not only been shown to be safe in patients with HF but can also improve renal function, enhance quality of life, increase LVEF, and decrease the risk of hospitalization and death. Use of other guideline-directed medical therapy is indicated in patients with HF regardless of diabetes status. ■ ■SLEEP APNEA Sleep-disordered breathing is common in HF, with increased incidence of both obstructive sleep apnea and central sleep apnea (Chap. 308). The pathophysiologic link between these disorders has been studied in both animal models and humans and includes increased afterload, decreased preload, intermittent hypoxia, and sympathetic activation. Increase in sympathetic tone can provoke ischemia and arrhythmias and complicate blood pressure management. Approximately one-third of patients with HF and sleep-disordered breathing have central sleep apnea, which is associated with increased mortality independent of other known risk factors. In patients with HFrEF and obstructive sleep apnea, continuous positive airway pressure has been shown to improve quality of life, decrease blood pressure and arrhythmias, and increase LVEF. Unlike obstructive sleep apnea, there is no proven therapy for central sleep apnea, although phrenic or hypoglossal nerve pacing may provide benefit in some cases. ■ ■OBESITY Similar to diabetes, obesity is both a risk factor for the development of HF and highly prevalent in patients with HF. In particular, obesity is common in patients with HFpEF and complicates the assessment of volume status in both ambulatory and inpatient settings. Unlike diabetes, the risk of morbidity and mortality in patients with obesity and HF is complex. The obesity paradox refers to the observation that obese patients diagnosed with HF have a more favorable prognosis than patients with low or even normal body mass index. While weight loss has been shown to improve quality of life and exercise capacity and may contribute to reverse ventricular remodeling in patients with HF, the impact on survival is unknown. Large randomized clinical trials are assessing safety and efficacy of glucagon-like peptide-1 (GLP-1) agonists such as semaglutide in patients with heart failure and obesity. ■ ■DEPRESSION Depression is an independent risk factor for adverse outcomes in HF (Table 264-1), especially in older women. The mechanisms

TABLE 264-8 Differential Diagnosis of Heart Failure SYMPTOM OR SIGN DIFFERENTIAL DIAGNOSIS Dyspnea Chronic lung disease Pulmonary arterial hypertension Neuromuscular disease Anemia Iron-deficiency anemia Edema Venous insufficiency Nephrotic syndrome Deep vein thrombosis Lymphedema Ascites Hepatic cirrhosis Portal vein thrombosis Malignant carcinomatosis Pleural effusion(s) Chronic infection Lung cancer Collagen vascular or rheumatologic disease Jugular venous distension Constrictive pericarditis Pericardial effusion Superior vena cava syndrome

underlying this risk remain unknown but may involve neuroendo crine dysfunction and systemic inflammation, as well as contribu tions from poor sleep, decreased appetite, and adverse effects of medications and alcohol. The AHA recommends screening for depression among patients with cardiovascular disease including HF using validated patient health questionnaires. Selective serotonin reuptake inhibitors are safe for treating depression in HF but do not appear to affect the natural history of disease. The effects of cognitive behavioral therapy and the collaborative care

model, as well as newer therapies such as transcranial magnetic stimulation, on HF morbidity and mortality require further study. DIFFERENTIAL DIAGNOSIS Many symptoms and signs suggesting HF may be caused by other conditions (Table 264-8). In a patient with dyspnea, the clinician must distinguish cardiac from pulmonary causes, although the differentiation may be difficult. For example, orthopnea may be a well-established symptom in some patients with severe chronic lung disease. Patients with underlying pulmonary disease may also experi ence episodic shortness of breath during sleep that mimics PND. In chronic lung disease, this is usually due to accumulation of tracheo bronchial secretions and is relieved by coughing and expectoration, whereas in cardiac disease, the patient has to sit upright. Wheezing caused by bronchoconstriction may be a prominent symptom when left ventricular failure supervenes in individuals with reactive airways disease. Patients with cardiac asthma may be more likely to exhibit diaphoresis and varying degrees of cyanosis compared to patients with bronchial asthma. Differentiating dyspnea related to HF versus pulmonary disease may be impossible when the diseases coexist, a situation that is common in chronically ill older patients with active or prior smoking. Following effective diuresis, pulmonary function tests may help to determine the predominant cause of dyspnea. In ambulatory patients with advanced HF, cardiopulmonary exercise testing can also help to make this distinction. Finally, a very low BNP or NT-proBNP level may be helpful in excluding HF as the cause of dyspnea in nonobese patients. Apart from pulmonary disease, HF needs to be distinguished from conditions in which congestion results from abnormal salt and water retention but in which cardiac structure and function are normal (e.g., acute or chronic kidney disease) and from noncardiac causes of pulmo nary edema (e.g., acute respiratory distress syndrome). Non-HF causes of lower extremity edema such as venous insufficiency, lymphedema, and obesity should also be considered.

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